REVIEW ARTICLE

ROLE OF DEPRESSION IN ALZHEIMER'S DISEASE

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ABSTRACT

Old age population in developing countries is rising as also chronic diseases like Alzheimer's disease (AD) with increase in morbidity and disability. Depression is considered increasingly both as a risk factor and prodromal feature in AD. Depression and Diabetes mellitus are now both considered as risk factors in conversion of Mild Cognitive Impairment (MCI) to AD with neuro-inflammation as a possible underlying cause. Cognitive deficits occurring in old age should be evaluated thoroughly and followed up at regular intervals.

Key words: Alzheimer's disease, depression, MCI, Risk, Prodrome.

Old age population according to world Alzheimer's report 2015 is currently 900 million people. Beyond the age of 60 years, mortality rates have been falling with increasing life expectancy and increased prevalence of chronic diseases. Higher fertility rates and decreasing mortality rates in developing countries is increasing old age population by at least 3 times compared to the developed nations.[1] Alzheimer's disease (AD) is one such chronic disease with global estimation in 2015 to be 46.8 million and projected to double by 2030. Risk factors for Dementia like obesity, hypertension, diabetes mellitus and dyslipedemia have impact on brain's health. A rise in cardiovascular risk factors and morbidity in low and middle income countries are likely to increase prevalence of dementia in future.

Disability affected Life Years (DALY's) due to dementia as per WHO global burden of disease (2004) contributes to 40% of the total DALY's.

Among the risk factors, Type 2 Diabetes mellitus and depression have been emerging as conditions linked to conversion of Mild Cognitive Impairment (MCI) to dementia. It is now fairly well documented that mood disorders are associated with cognitive dysfunction[2] - Impairments in attention, processing speed and executive function have been noticed in acute as well as in remitted phases.[3] Hippocampal atrophy[4,5] and white matter changes[6] have been noticed especially in late onset depression. Cognitive impairments have not been shown to improve totally with antidepressant treatment. There was no improvement in cognitive functions with anti-depressant therapy and thereby cognitive impairment needs to be considered seriously and should not be dismissed as pseudodementia. Cache County study – a population study of memory, health and ageing found that the cumulative prevalence of depression in dementia in 5-yr period was 77%.[7]

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Depression as a prodrome of dementia:

Saira Saeed Mirza et al, 2013[8] reports of 8% increased risk of dementia in 582 subjects with depression in a 13.7 year long follow up study. Late onset depressive symptoms represent a part of prodromal stage of dementia. Jost et al 1996[9] in a retrospective study of frequency of occurrence of behavioural symptoms preceding and following Alzheimer's disease in 100 subjects, noticed depression in 60%, occurring at least 2 years before the onset of AD. Irritability, anxiety and other mood changes and diurnal rhythm changes occur around the time of making AD diagnosis.

Late onset Depression (LLD):

First episode of depression occurring after the age of 65 is considered as late onset or geriatric depression and it is advised to search for structural brain abnormalities of vascular origin. Also severe depression and psychotic features were reported to be more prevalent in LLD.[10] Recurrent depressive episodes confer higher rate for development of dementia. Kessing et al,[11] notice that the rate of dementia increased by 13% with every recurring episode of depression in dementia. In a prospective study by Dotsun et al,[12] depression was associated with increasing dementia by 14% in a 2 year interval period.

Assessment of Depression in patients with Dementia:

Geriatric depression scale (GDS) could be difficult to administer due to communication problems or aphasia in the event of stroke. Cornell scale for depression in

Dementia (CSDD) relies on interview with patients, carers and direct observation. It has 19 items with a rating 0= absent, 1= mild, 2= severe. Summed up scores of 8 or more indicates depression.[13] Poor performance on measures of executive functioning and cognitive inhibition predict poor antidepressant response, with relapses and higher functional disability. Decreased grey matter volume in anterior cingulate cortex and its functional connections with dorsolateral prefrontal cortex is also another reason for poor response.[14,15] A subgroup of elderly patients present with 'depression-executive dysfunction' (DED) syndrome characterized by psychomotor retardation, anhedonia, apathy, mild vegetative symptoms and functional disability which is disproportionate to depressive syndrome and it is due to medial frontal lobe deficits.

Role of Antidepressants in treatment of depression and control of dementia:

Antidepressants have neuroprotective action by proliferation of neural progenitors in hippocampus thereby improving memory process and cognition. Whether this can be generalized to dementia is to be seen. Register based studies show decreased rates of dementia with use of antidepressants for all classes (SSRI, SNRI and TCAs). However, there are also clinical studies which do not subscribe to this point of view.

Moreover good number of geriatric depression patients are left with residual depressive symptoms and neuropsychological deficits after antidepressant treatment.[16]

Cognitive Remediation for LLD:

The basis for remediation is neuroplasticity. Neuroplasticity based computerized Cognitive remediation (N-CCR) is been under active consideration however evidence is lacking in this area.

LLD as a risk of incidence in AD and Vascular Dementia:

Breno et al.,[17] in a meta-analysis of 23 studies on 49 612 patients out of whom 5116 developed LLD. Pooled Hazard ratios for vascular dementia (2.52, 95% C.I 1.71- 3.59, P<0.001), AD (1.65, 95% CI 1.42-1.92, p<0.001 and other dementias (1.85, 95% C.I 1.67- 2.04, P<0.001)

Geriatric presentation of depression:

Compared to adult depression, geriatric depression presents with fatigue, hopelessness, anger, anxiety, irritability and thoughts of death, Somatic symptoms overlap with co morbid disease and medication.[18]

Cognitive decline and dementia in elderly with diabetes mellitus:

Studies have demonstrated a link between poor glycemic control and deteriorating cognitive function in diabetic patients. Depression is known to decrease compliance to medication use and life style intervention. Proinflammatory cytokines are also released in depression which have also been noticed in dementia.[19]

In LLD, MCI, Dementia - Is inflammation the missing link? MCI is an intermediate stage between cognitive changes of normal aging and dementia. Prevalence of MCI above 70 years is reported to be 14 – 18% and the rate of progression to dementia (AD) is estimated at 10-15% per year. Depressed patients were found to have higher levels of C reactive protein (CRP), proinflammatory cytokines suggestive of excessive inflammation. Senile plaques and neurofibrillary tangles in AD are associated with raised proinflammatory markers. Studies have reported higher serum levels of inflammatory cytokines IL-6, IL2 and TNF-alpha in depression as well as in AD suggestive of chronic inflammatory changes.[20,21]

In a meta-analysis by Claudia Cooper,[22] on modifiable predictors of dementia in MCI, pooled odds ratio in 13 studies for having depressive symptoms was (1.35, 95% CI 0.89 – 2.06). There is grade 1evidence that more depressive symptoms predict conversion from MCI to all causes of dementia in epidemiological studies.

Stefan van der Mussele[23] in a longitudinal follow up study of 183 MCI subjects for 9 years reported significant depressive symptoms in MCI (HR: 2.06; 95% C.I 1.23 – 3.44) on CSDD. Also severity of depressive symptoms was a predictor for progression of MCI. A meta-analysis of longitudinal studies for depression as a risk factor for dementia and MCI by Yuan Gao,[24] reported subjects with depression had higher incidence of AD (RR: 1.66, 95% C.I 1.29 – 2.140, and for VaD 2 studies (RR 1.89, 95% CI, 1,19 - 3.01).

CONCLUSIONS

Depression has been seen to proceed at least 2 years before the onset of Alzheimer's disease. Late onset depression can be considered as a prodromal feature for AD. Cognitive deficits seen in LLD which are refractory to treatment should be carefully followed up and should not be disregarded as it indicates early features of dementia. Neuroinflammation could be a common link between depression, diabetes mellitus and AD, which is currently an active area for research. Epidemiological studies suggest that there is a grade I evidence for conversion of MCI to dementia.

Screening, early recognition and treatment of depression occurring in old age should be done regularly by physicians.

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